## REMARKS

Before this Amendment, claims 35-69 were pending. By this Amendment, claims 40-69 have been canceled, solely in response to the Restriction Requirement. Accordingly, claims 35-39 are pending.

Claim 35 has been amended to recite "with a salt content of less than 10% by weight." Support for this amendment is found in the specification, at page 20, lines 16-17: "It is preferable that the high purity compound of the general Formula libe present in the form of the free base with a combined salt part of less than 10 percent by weight ..."

The rejection under 35 U.S.C. §103(a)

Claims 35-39 were rejected as being obvious over WO 99/58478 (Claus) and WO 94/11337 (Arne).

According to the Office Action, Claus teaches the claimed compounds, although not at the level of purity claimed. Arne, at page 11, lines 15-25, teaches related compounds in high purity (>99%) as assessed by chromatography. It would therefore have been prima facie obvious to combine Claus with Arne to arrive at the claimed compounds at the claimed level of purity.

The Applicants respectfully traverse this rejection.

The Office Action is incorrect in several respects. First, Arne's disclosure is not relevant to the present claims. The portion of Arne referred to, page 11, lines 15-25, refers only to optical purity. See page 11, lines 20-21: "The optical purity as assessed by chromatography was >99%." Optical purity is an entirely different type of purity from that

recited in the present claims. Thus, the disclosure in Arne is not relevant to the issue of the purity of a compound defined as "a free base with a salt content of less than 10% by weight and in a degree of purity of above 97 percent by weight," as in the presently amended claims. In fact, claim 35 specifically states that the claimed compound need not be optically pure ("where the C-atom marked with a star "*" may be present in the (R)-configuration, the (S)-configuration or as a mixture of such configurations.")

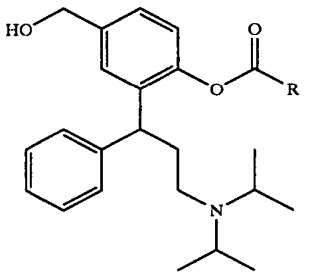
The Applicants also note that, although the Office Action states that one of ordinary skill in the art would use the chromatography techniques of Arne to obtain the claimed compounds in pure form, Arne actually used chromatography in the passage cited (page 11, lines 15-25) only to assess optical purity, not to obtain a compound in optically pure form. To obtain optically pure compounds, Arne used the conventional process of differential crystallization of each optical isomer, using optically active forms of tartaric acid. It is clear that such a process would be of no help to make free bases in highly pure form.

Accordingly, there is no disclosure or suggestion in Arne how to achieve the presently claimed compounds in highly pure base form.

Second, the prior art taught away from the present claims. The claims have been amended to clarify that the claimed free base compounds in high purity have a salt content of less than 10% by weight. The prior art taught away from the use of the free base of the claimed compounds in high purity with such a low salt content because the prior art preferred the claimed compounds as stable salts. See, e.g., Exhibit A (U.S. Patent No. 6,858,650).

U.S. Patent No. 6,858,650 teaches that compounds similar to those of the present claims, in their basic form, are disadvantageous. See col. 1, ll. 30-49:

Formula A




in which R denotes $C_1$–$C_6$-alkyl, $C_3$–$C_{10}$-cycloalkyl or unsubstituted or substituted phenyl. These can occur in their optical isomers form as racemic mixtures and in the form of their individual enantiomers.

Compounds with the structure of formula A do, however, have low solubility in water. This restricts their oral bio-availability.

U.S. Patent No. 6,858,650 goes on to propose that the problems with these compounds can be overcome by the use of stable salt forms of the compounds. See col. 2, ll. 17-22:

> The problem for the present invention is therefore to provide highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, that avoid the stated disadvantages and are well suited to use in pharmaceutical-technical formulations and can be processed into these.

Thus, one of ordinary skill in the art, coming upon the disclosures of Arne, would not have applied Arne's disclosures to the compounds of Claus in order to obtain highly pure free bases because the prior art taught that free bases of the claimed compounds should be avoided in favor of the salts.

Third, even if the above argument from the Office Action is correct, and a *prima facie* case of obviousness has been made out, claims 35-39 are non-obvious because the compounds of claims 35-39 show unexpected, superior results compared to the closest prior art compounds. The salts of the prior art and the claimed compounds were formulated into compositions suitable for transdermal delivery. When the salts of the prior art were then

compared with one of the claimed compounds for their transdermal flux rates, it was found that the claimed compound, in highly pure free base form, with less than 10% salt content by weight, was vastly superior to the prior art compounds. See paragraphs 116-118 and Table 2 of U.S. Patent Publication No. 2006/0014832 (the publication of the present application):

> **[0116]** It is preferable that the high purity compound of the general Formula Ibe present in the form of the free base with a combined salt part of less than 10 percent by weight, especially preferable less than 5% or 3%, notably especially preferable less than 1%.
>
> **[0117]** If the high purity salts from 3,3-diphenylpropylamine derivates known from WO 01/35957, for example, the fumarate salt from fesoterodine, only lead in the case of transdermal delivery to flux rates not sufficient for transdermal treatment, even the addition of loaded molecules such as silicates or Chitosan, for example, or of skin penetration amplifiers like oleic acid or PGML (polyglycol monolaurate) to the matrices containing the active ingredient salt does not lead to satisfactory flux rates (Table 2).
>
> **[0118]** Even an in-situ release of the base from the corresponding salt through the addition of calcium silicate during manufacture of the adhesive matrix, as described in WO 94/07486, does not lead to the flux rates through the human skin desired (Table 2), because the in-situ conversion to the free base is generally not absolute so that too high a proportion of the active ingredient in its protonated form is present in the matrix.

TABLE 2

| Lot-No | Contact adhesive | Procedure | Loading of the active ingredient (Percent by weight fesoterodine) | Matrix weight ($g/m^2$) | Flux $\mu g/cm^2$/Day (in steady state; after 24 hours) Mouse Skin | Human skin |
|---|---|---|---|---|---|---|
| 20111080[1] | Acrylate | Solvent | 15 | 100 | 705 | n.d. |
| 20302060[1] | Acrylate | Solvent | 15 | 87 | n.d. | 332.64 |
| 20111085[1] | EVA | Hot melt | 15 | 84 | 510 | 323.7 |
| 20111086[1] | Silicone | Hotmelt | 15 | 63 | 495 | n.d. |
| 20302062[1] | Silicone | Hotmelt | 15 | 100 | n.d. | 544.89 |
| 20111087[1] | SxS | Hotmelt | 15 | 89 | 460 | 383.8 |
| 20302063[1] | Silicone + PVAc[6] | Hotmelt | 15 | 83 | n.d. | 501.09 |
| 20002031[2] | Acrylate | Solvent | 15 Fumarate | 105 | 27 | n.d. |
| 20104035[2,3] | Acrylate/OL | Solvent | 15 Fumarate | 110 | 84 | n.d. |
| 20106061[4] | Silicone | Solvent | 15 Fumarate | 60 | n.d. | 24,2 |
| 20106043[5] | Silicone | Hotmelt | 15 DiOH[5] | 101 | n.d. | 2,3 |

n.d. = not determined;

[1]= fesoterodine was added to the matrix as the free base;

[2]= Comparison example manufactured through the use of fesoterodine-fumarate salt;

[3]= Comparison example manufactured through the use of fesoterodine-fumarate salt with oleic acid as the permeation enhancer;

[4]= Comparison example manufactured through the in-situ release of the base from the fumarate salt into the adhesive matrix;

[5]= Comparison example manufactured through the use of the dihydroxymetabolites (2-[3-(1,1-diisopropylamino)-1-phenylpropyl]-4-(hydroxy methyl)phenol) from fesoterodine;

[6]PVAc = Poly Vinyl Acetate.

In view of the above, it is respectfully requested that this rejection be withdrawn.

The time for responding to the Office Action was set for August 31, 2007. Enclosed herewith is a Petition for the Extension of Time under 37 C.F.R. § 1.136(a) for a period sufficient to permit the filing of this paper. Charge any fees associated with the Petition for the Extension of Time to Kenyon & Kenyon's Deposit Account No. 11-0600.

The Applicants hereby make a Conditional Petition for any relief available to correct any defect seen in connection with this filing, or any defect seen to be remaining in this application after this filing. The Commissioner is authorized to charge Kenyon & Kenyon's

Deposit Account No. 11-0600 for the Petition fee and any other fees required to effect this Conditional Petition.

Respectfully Submitted,

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